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〈医用工学部研究論文〉

In vivo disposition of *S*-(1,2-dichlorovinyl)-*L*-cysteine in mice

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Abstract

S-(1,2-dichlorovinyl)-*L*-cysteine (DCVC) is known to cause renal-cellular injury after metabolic activation by cysteine conjugate *β*-lyase and to exert *in vitro* toxicity against bone-related cell lines. However, little is known about the *in vivo* disposition of DCVC in mice.

We studied the *in vivo* disposition of [^{35}S] DCVC in mice after intraperitoneal administration at a dose of 30 mg/kg. DCVC and its related substances were well absorbed rapidly, distributed highly in the kidneys, and then slowly eliminated from the body. The concentration of DCVC and its related substances was the highest in the femoral epiphysis in the bone tissues examined. The main excretion route was the urine.

Introduction

Trichloroethylene (TCE) is generally used as synthetic material for alternative fluorocarbon or metal-degreasing agent. It is designated as a Class II Specified Chemical Substance, and required to be controlled under the guideline for environment conservation. Several studies revealed TCE toxicity in mice, rats and humans. [1), 2)] TCE is metabolized in several pathways including glutathione (GSH)-dependent metabolism through which TCE is metabolized into DCVC [3)]. DCVC is considered to produce renal-cellular injury after metabolic activation by cystaine conjugate *β*-lyase [3)]. In mice, toxicity of DCVC against cultured bone cells such as chondrocytes, osteoblasts and osteoclasts *in vitro* [4)], decrease in bone density *in vivo* [5)] and nephrotoxic effect of subchronic in mice [6)] are reported. However, little is known about the *in vivo* disposition and distribution into the bone tissues of DCVC in mice.

Objective

The concentration-time profiles of DCVC-related substances in blood, the excretion of DCVC-related substances in urine and feces, and the distribution of DCVC-related substances in tissues, especially the distribution

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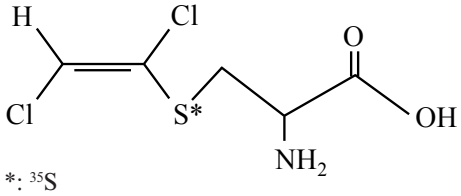
into the bone tissues, were investigated after single intraperitoneal administration of [^{35}S] DCVC to male mice.

Material and Methods

Material



*: ^{35}S

A portion of [^{35}S]DCVC (Radiochemical purity: 98.6%) was suspended in physiological saline to prepare a dosing formulation at a concentration of 6 mg/2.42 MBq/mL. The dosing formulation was administered intraperitoneally to non-fasted male Balb/c mice at 6 weeks of age (Charles River Laboratories Japan, Inc.) at a dose of 30 mg/kg. The blood was collected at 0.25, 0.5, 1, 2, 4, 8, 24 and 48 h. The urine and feces were collected at 0-24 and 24-48 h. The tissues were collected at 24 h. The samples were measured for radioactivity by liquid scintillation counting after dissolution with SOLUENE®-350. The concentration of radioactivity in the blood and tissues (μg equiv./g or mL) and the excretion ratio in urine and feces (% of dose) were calculated.

Results and Discussion

1. Concentration-time profile of radioactivity in blood

After single intraperitoneal administration of [^{35}S]DCVC at a dose of 30 mg/kg to non-fasted male mice, the blood concentration of radioactivity reached C_{max} (12.2 μg equiv./mL) at 0.5 h and decreased to 6.3 μg equiv./mL by 24 h, followed by a decreased to 3.8 μg equiv./mL by 48 h with $t_{1/2}$* of 36.2 h (*Figure 1*).

*: Time points used for the calculation of $t_{1/2}$ value were 8 to 48 h.

2. Distribution of radioactivity in the tissues

In the tissues at 24 h after administration, the concentration of radioactivity was the highest in the kidneys (154.7 μg equiv./g, tissue/plasma ratio: 17.7). The concentrations were, in descending order, higher in the pancreas, liver, stomach, femoral epiphysis and heart (from 32.6 to 10.0 μg equiv./g) than in the plasma (8.9 μg equiv./mL) (*Figure 2*).

The concentrations in the other tissues were 8.1 μg eq./g or mL or less. In the bone tissues, the concentration of radioactivity was the highest in the femoral epiphysis (10.0 μg equiv./g). The concentrations in the parietal, vertebra and femoral diaphysis were 4.1, 5.7 and 4.7 μg equiv./g, respectively. (*Figure 3*)

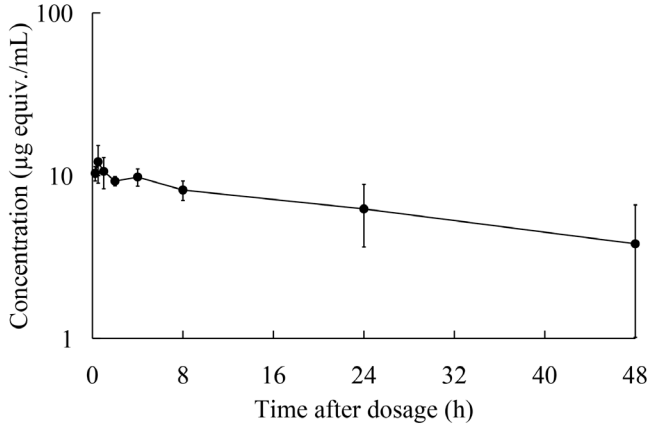


Figure 1

Concentration of radioactivity in the blood of male mice after single intraperitoneal administration of [^{35}S]DCVC at a dose of 30 mg/12.1 MBq/kg.

Each point with a vertical line represents the mean and SD for three animals.

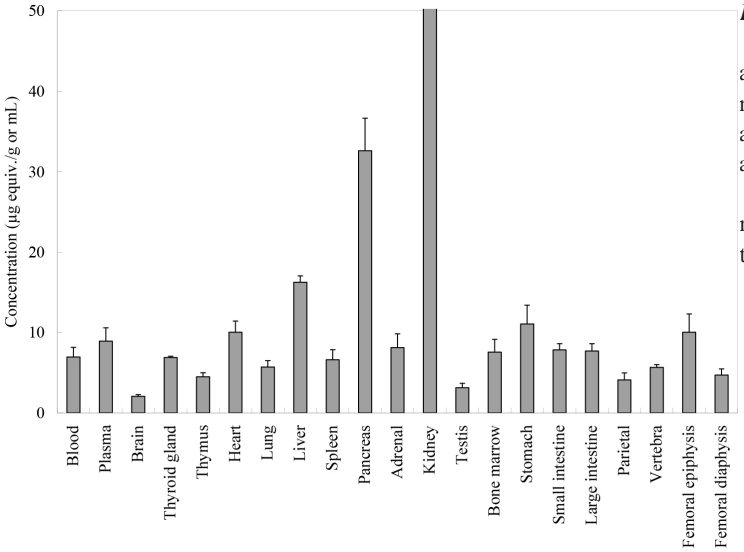


Figure 2

Concentration of radioactivity in the tissues of male mice after single intraperitoneal administration of [^{35}S]DCVC at a dose of 30 mg/12.1 MBq/kg.

Each value and vertical line represents the mean and SD for three animals.

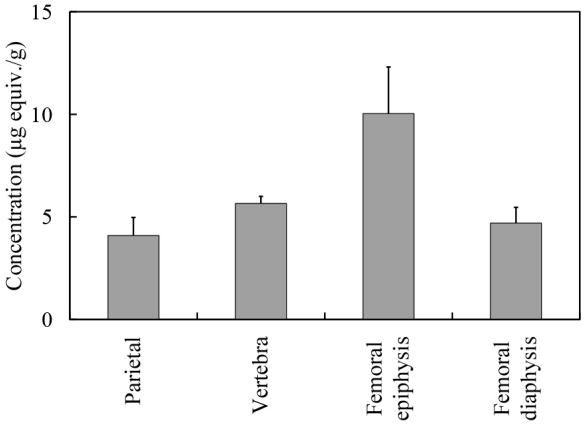


Figure 3

Concentration of radioactivity in the bones of male mice after single intraperitoneal administration of [^{35}S]DCVC at a dose of 30 mg/12.1 MBq/kg.

Each value and vertical line represents the mean and SD for three animals.

3. Urinary and fecal excretion

The cumulative excretion ratios of the radioactivity into the urine and feces by 48 h after intraperitoneal administration were 50.7% ± 6.2% and 6.9% ± 6.0% to the dose, respectively, and the sum of the cumulative excretion ratios was 57.6% ± 11.9% (*Table 1*).

These results indicated that DCVC and its related substances were well absorbed at a relatively fast rate, and then slowly eliminated from the blood after intraperitoneal administration of [^{35}S]DCVC to mice. DCVC and its related substances were mainly excreted into the urine.

Table 1

Cumulative excretion of radioactivity in the urine and feces of male mice after single intraperitoneal administration of [^{35}S]DCVC at a dose of 30 mg/12.1 MBq/kg.

Specimen	Time after dosage (h)	Cumulative excretion of radioactivity (% of dose)	
		Mean	SD
Urine	24	39.0	7.8
	48	50.7	6.2
Feces	24	3.6	3.4
	48	6.9	6.0
Total	24	42.6	11.0
	48	57.6	11.9

Each value represents the mean and SD for three animals.

DCVC and its related substances were distributed widely into the tissues especially highly in the kidneys. In the several bone tissues examined, the concentration in the femoral epiphysis was approximately two times the concentration in each of the other bone tissues.

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